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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(31) International Patent Classification 6: A61K 31/70, A61F 13/20, G02C 7/02		A1	(11) International Publication Number: WO 95/07085 (43) International Publication Date: 16 March 1995 (16.03.95)
(21) International Application Number: PCT/US94/10175 (22) International Filing Date: 7 September 1994 (07.09.94)		(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(30) Priority Data: 08/116,908 7 September 1993 (07.09.93) US		Published <i>With international search report</i>	
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(54) Title: SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

(57) Abstract

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grade viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm², particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.

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1 SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

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3 This application is a continuation-in-part of copending
4 U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a
5 continuation of U.S. Pat. App. 07/440,078 filed November 22,
6 1989, now abandoned.

7

8

Field of the Invention.

9 The present invention relates to ophthalmic solutions for
10 use during ocular and intraocular surgery, and more particularly
11 to the use of surface active viscoelastic solutions during the
12 extraction of a cataractous human lens and the implantation of a
13 prosthetic ocular and intraocular lens. During surgery, the use
14 of ophthalmic infusions with controlled physical properties,
15 especially surface activity and viscoelastic properties, is
16 advantageous for (1) replacing the fluid aqueous humor or ocular
17 and intraocular air, (2) protecting the internal structures of
18 the eye from accidental instrument or ocular and intraocular
19 prosthetic device contact, (3) preventing irrigation damage by
20 solutions used in routine cataract surgery, and (4) retarding
21 aspiration from the eye of the viscoelastic solution during the
22 surgical procedure. In addition, the invention relates to a
23 method of adhering a contact lens to the surface of the eye,
24 such as in association with procedures permitting a medical
25 professional to view ocular and intraocular structures through
26 the contact lens and through the viscoelastic solution. In

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1 another application, the viscoelastic solution of this invention
2 is used by injecting the solution into or under tissues within
3 the eye, such as to dissect tissue off of the retina.

4 **Background of the Invention**

5 In the past, biocompatible polymers used in ocular and
6 intraocular surgery have been the naturally occurring
7 mucopolysaccharides hyaluronic acid and chondroitin sulfate;
8 mixtures of hyaluronic acid and chondroitin sulfate; and,
9 cellulose derivatives, such as hydroxypropylmethylcellulose
10 (HPMC). Table 1

11 presents data reported in Viscoelastic Materials, Ed. E.S.
12 Rosen, Proceedings of the Second International Symposium of the
13 Northern Eye Institute, Manchester [U.K.], 17-19 July, 1986
14 (Pergamon Press, New York) as to the molecular weight of
15 commercially available ocular products. Depending on the source
16 from which these mucopolysaccharides are drawn, the molecular
17 weights are estimated in the 50,000 range with the hyaluronic
18 acid extending upwards to the 8×10^6 range. Hyaluronic acid
19 was first isolated and characterized by Meyer, Palmer and
20 reported in the J. Biol. Chem., Vol. 107, p. 629 (1934) and Vol.
21 114, p. 689 (1936) and by Balazs in the Fed. Proc., Vol. 17, p.
22 1086 (1958); and chondroitin sulfate by Bray et al. in Biochem.
23 J. Vol. 38, p. 144 (1944); and Patat, Elias, Z. Physiol. Chem.
24 vol. 316, p. 1 (1959).

25
26 Literature in the art describes the basic isolation and
27 characterization of the viscoelastic solutions. It is a
28 surprising feature of this invention which describes the control

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1 of viscoelastic properties as related to the surface activity,
2 or the solution fracturing under applied stress. In particular,
3 it is surprising to manipulate or enhance the physical
4 properties of viscoelastic solutions of mucopolysaccharides,
5 hyaluronic acid, and/or chondroitin sulfate. It is believed
6 that disclosure here of a processes to provide hyaluronic acid
7 and species thereof with controlled surface activity is unique.
8 This is also especially true of the control of surface activity
9 of mucopolysaccharide solutions by the addition of biologically
10 compatible surfactants. A characteristic feature of
11 biologically compatible surfactants is the absence of observed
12 alteration in cellular physiology upon contact. Early work in
13 the viscoelastic field was presented by the inventor of this
14 disclosure and his associates. Benedetto, D.A. et. al.,
15 Viscoelastic Materials: Basic Science and Clinical Application,
16 (Symposium Proceedings), University of Manchester, England, July
17 17-19, 1986.

18
19 As to commercial production, a review of the ophthalmic
20 pharmacopoeia reveals there are several viscoelastic solutions
21 produced for ocular and intraocular use during ophthalmic
22 surgery. The most common application for these solutions is in
23 the intraocular lens implant procedure for human cataract
24 surgery. This procedure involves extraction of the cataractous
25 human lens through a small surgical opening in the eye and the
26 replacement of the lens by a prosthetic intraocular lens placed
27 in situ. Biocompatible polymers presently or previously in use
28 are hyaluronic acid (Healon™, Amvisc™); chondroitin sulfate, and

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1 a combined solution of hyaluronic acid and chondroitin sulfate
2 (Viscoat™); and a hydroxypropylmethylcellulose solution
3 (Occucoat™). Research conducted recently demonstrates that
4 Healon™ and Amvisc™ are not surface active, but Viscoat™ and
5 Occucoat™ are.

6 Chondroitin sulfate does not exist as a free polysaccharide
7 in its native state, but as a proteoglycan. It is obtained from
8 sources associated with protein contaminants. The avoidance of
9 chondroitin sulfate avoids a potential source of pyrogenic
10 reaction, and the substantial cost associated with protein
11 removal.

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13 Summary of the Invention

14 The invention presented herein discloses modified
15 mucopolysaccharide or viscoelastic solutions for use as
16 biologically active therapeutic infusions. In one form of the
17 invention, the mucopolysaccharide solution is formed from a
18 viscoelastic fraction and a buffer fraction. It has been found
19 that when a new synthetic molecule acyl-substituted hyaluronic
20 acid is employed as the viscoelastic fraction, control of
21 surface activity is achieved. An indicia of this is the
22 decrease of the surface tension of the solution which is now
23 within predetermined limits discussed below. Surface tension
24 modification is also accomplished with viscoelastic fractions in
25 which the acyl-substituted hyaluronic acid is mixed with one or
26 more of hyaluronic acid; and hydroxypropylmethylcellulose. In
27 certain applications, the viscoelastic solution of this
28 invention is used in a method of adhering a contact lens to the

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1 surface of the eye, such as in association with procedures
2 permitting a medical professional to view ocular and intraocular
3 structures through the contact lens and through the viscoelastic
4 solution. This is particularly useful in facilitating surgical
5 procedures. In another application, the viscoelastic solution of